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Impact of UVA on pruritus during UVA/B-phototherapy of inflammatory skin diseases : a randomized double-blind study

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Abstract: BACKGROUND Narrowband (TL-01) UVB phototherapy (UVB nb) is effective in treating inflammatory skin disease. The addition of UVA is traditionally advocated to reduce pruritus, but lacks evidence for this recommendation. OBJECTIVES The aim of this study was to assess the effect of UVB nb and UVA phototherapy in combination compared against UVB nb monotherapy on pruritus, disease activity, and quality of life. METHODS In this double-blind randomised clinical trial 53 patients suffering from inflammatory skin diseases with pronounced itching (Visual Analogue Scale (VAS) for pruritus 5) were randomised in to two treatment groups. One group received UVB nb (311nm) phototherapy alone and another group received a combination of UVB nb and UVA (320-400nm) phototherapy. UV therapy was performed three times per week over 16 weeks. Pruritus (VAS and 5-D itch score), disease activity and quality of life (Dermatology Life Quality Index, DLQI) were assessed at baseline and weeks 4, 8, 12, and 16. RESULTS In both treatment groups there was a reduction in pruritus scores, disease activity and DLQI. No difference in pruritus score, disease activity, and quality of life could be detected between the group receiving UVB nb alone and those receiving UVB nb combined with UVA. CONCLUSIONS Phototherapy with UVB nb and UVB nb combined with UVA are equally effective in treating inflammatory skin disease and indifferent in reducing disease-associated pruritus. Given this non-inferiority for UVB nb monotherapy, the recommendation of adding UVA to UVB nb phototherapy for pruritic inflammatory skin disease should be abandoned.

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Impact of UVA on pruritus during UVA/B-phototherapy of inflammatory skin diseases - a randomized double-blind study

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Author Contributions:

- Maul and Kretschmer had full access to all of the data of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
- *Study concept and design:* Hofbauer, Navarini.
- *Acquisition of data:* Maul, Kretschmer.
- *Analysis and interpretation of data:* Maul, Kretschmer, Navarini.
- *Drafting of the manuscript:* Maul, Kretschmer, Pink, Hofbauer, Navarini.
- *Critical revision of the manuscript for important intellectual content:* Anzengruber, Murer, French.
- *Study supervision:* Hofbauer, Navarini.

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Abstract

Background Narrowband (TL-01) UVB phototherapy (UVB nb) is effective in treating inflammatory skin disease. The addition of UVA is traditionally advocated to reduce pruritus, but lacks evidence for this recommendation.

Objectives The aim of this study was to assess the effect of UVB nb and UVA phototherapy in combination compared against UVB nb monotherapy on pruritus, disease activity, and quality of life.

Methods In this double-blind randomised clinical trial 53 patients suffering from inflammatory skin diseases with pronounced itching (Visual Analogue Scale (VAS) for pruritus ≥ 5) were randomised in to two treatment groups. One group received UVB nb (311nm) phototherapy alone and another group received a combination of UVB nb and UVA (320-400nm) phototherapy. UV therapy was performed three times per week over 16 weeks. Pruritus (VAS and 5-D itch score), disease activity and quality of life (Dermatology Life Quality Index, DLQI) were assessed at baseline and weeks 4, 8, 12, and 16.

Results In both treatment groups there was a reduction in pruritus scores, disease activity and DLQI. No difference in pruritus score, disease activity, and quality of life could be detected between the group receiving UVB nb alone and those receiving UVB nb combined with UVA.

Conclusions Phototherapy with UVB nb and UVB nb combined with UVA are equally effective in treating inflammatory skin disease and indifferent in reducing disease-associated pruritus. Given this non-inferiority for UVB nb monotherapy, the recommendation of adding UVA to UVB nb phototherapy for pruritic inflammatory skin disease should be abandoned.

Introduction

Vexing pruritus is a disturbing and highly prevalent symptom associated with many inflammatory skin diseases. It is a major diagnostic criterion for atopic dermatitis[1] and affects 84% of patients suffering from psoriasis, .[2] The impact of pruritus on health-related quality of life (QoL) is comparable to patients suffering from chronic pain.[3, 4] Effective therapies are therefore critically needed, and phototherapy is generally acknowledged to provide an important contribution in reducing pruritus.[5] Distinct types of ultraviolet (UV) radiation are routinely used, long-wave UVA,[6] short-wave UVB nb,[7] or a combination of both (UVB nb and UVA).[8] As all these types are suitable for treating inflammatory skin diseases, the actual choice of radiation appears insignificant. However, different mechanisms by which the generation of pruritus can be inhibited have been discussed, and are generally linked to the penetration depth of UV into the affected skin. UVB is thought to mainly affect epidermal keratinocytes and Langerhans cells, while UVA can also affect dermal T lymphocytes, mast cells, fibroblasts and dendritic cells.[9] Both types of UV radiation are able to alleviate histamine-induced pruritus in healthy volunteers, but an additional induction of hyposensitivity to pruritic stimuli has been proposed for UVB.[10] In addition, an *in vitro* study showed that UVA and UVB radiation are both able to inhibit histamine release from mast cells, but only UVA can inhibit histamine release from basophils.[11] A further layer of complexity is added by the systemic effects of UV on immune function, which can be seen in half-body irradiation studies.[8] From these findings, it can be hypothesized that UVA and UVB radiation possess a distinct intrinsic potential to reduce pruritus, or could even have an additive effect when combined. Whether this is true in day-to-day clinical UV treatment of inflammatory skin diseases remains unknown however.

In this study we investigated the benefit of combination UVB nb and UVA phototherapy versus UVB nb monophototherapy in relieving pruritus, reducing disease activity, and improving the QoL of patients affected by various pruritic inflammatory skin diseases.

Materials and methods

Patients

This randomised double-blind clinical trial (ClinicalTrials.gov identifier: NCT01254240) was performed in the outpatient clinic, Department of Dermatology, University Hospital Zurich, between 2010 and 2015. Eligible patients were all over the age of 18 years, suffered from inflammatory skin disease (e.g. atopic dermatitis, other eczema subtypes, psoriasis, prurigo simplex subacuta, and others (see table 1)), had pruritus VAS scores ≥ 5 , and had an indication for phototherapy. Exclusion criteria included foreseeable interruption of the light therapy for more than 14 days. Patients were further excluded if they displayed heightened photosensitivity to UVA or UVB, withdrew their consent to participate, concomitantly participated in another study or had taken part in another clinical study within the last 30 days.

The study was performed in accordance with the Declaration of Helsinki principles, and was approved by the Medical Ethics Committee of Zurich. All participants gave oral and written informed consent.

Study design

Patients included in the study were randomized in a 1:1 ratio in to two treatment arms (Fig. 1). One group received phototherapy with UVB nb (311nm) and another group received a combination of UVB nb and UVA (UVB nb/UVA; 320-400nm). Therapy was performed three times per week over a course of 16 weeks. At baseline, start of therapy and at 4, 8, 12, and 16 weeks, pruritus (VAS and 5-D itch score), disease activity (PASI, EASI, PGA, DDV respectively), as well as QoL (DLQI) were assessed. Where indicated, last-observation-carried-forward (LOCF) analysis was used to impute missing data.[12] Randomization was performed with sealed envelopes. Patients and investigators were blinded concerning treatment assignment.

Dosages and administration

Phototherapy was performed in the physical therapy unit of the Department of Dermatology in accordance with the standard light therapy protocol, as previously described.[13] Briefly, UVB nb treatment is started at a dosage of 0.1J/cm². In the absence of side effects, such as UV-induced erythema, the dosage was increased in increments of 20% per session, to a maximum dosage of 2.0 J/cm². Phototherapy was typically administered over a time course of 16 weeks, with 3 treatment sessions per week. For UVB nb/UVA treatment, UVA was additionally administered at a dosage of 0.5 J/cm² during standard UVB nb treatment, and was increased in increments of 20%, to a maximum dosage of 5.0 J/cm².

Phototherapy was performed with a UVB nb light cabin (Model UV7001, Waldmann [Waldmann Lichttechnik GmbH, Küttingen, Switzerland], output 310-315nm), and UVA/UVB nb light cabin (Model UV7002, Waldmann, UVA output 320-410nm, peak 351nm; UVB output 310-315nm, peak 311nm). The radiation sources irradiated all body surface areas with equal intensity.

Efficacy and safety measures

The primary efficacy endpoint was pruritus score change after completion of phototherapy at 16 weeks, as assessed by VAS and 5-D itch score. Secondary endpoints were disease activity (PASI, EASI, PGA, DDV respectively), and health-related QoL (DLQI questionnaire). At each study visit, patients received a physical examination and were screened for adverse events.

Statistical methods

Statistical analysis was performed with Prism 5.0 for windows (GraphPad Software, La Jolla, USA). Normality distribution of the data was assessed with the D'Agostino-Pearson omnibus test. P-values were calculated using the Student's t-test and the Mann-Whitney test, as indicated in the figure legends. Fisher's exact test and Chi-

square test were used to compare the baseline characteristics of both treatment groups from contingency tables. Bars depict the mean.

Results

A total of 53 patients were enrolled in the study (UVB nb, n=27; UVB nb/UVA, n=26). 45 patients completed the trial and were analysed at week 16 (UVB nb, n= 24; UVB nb/UVA, n=21). Due to loss of follow-up after the first study visit, 3 patients in the UVB nb treatment group, and 5 patients in the UVB nb/UVA treatment group were excluded due to work-related, private or withheld reasons, but none because of adverse events. Baseline characteristics were similar across both treatment arms (Table 1), with the vast majority of patients in both groups suffering from different forms of eczema (53,8%), psoriasis (25,0%), prurigo simplex subacuta (7,7%), and pruritus sine materia (3,8%). At baseline 40,9% of patients reported a history of previous phototherapy. *No severe adverse events occurred, three adverse events were recorded, namely two exacerbations during UVB nb/UVA treatment (one atopic eczema and one lichen planus). A third patient with atopic eczema developed suberythroderma and regressed after continuation of the phototherapy. No adverse events were seen in the UVB nb treatment group. The difference between both treatment groups was not significant ($p < 0.112$).*

In order to assess pruritus within our patient population, simultaneous monitoring via the visual analogue scale (VAS),[14] and the 5-D itch score [15] was chosen. Compared to the one-dimensional quantification of pruritus intensity, the latter score has the additional advantage of additionally quantifying the duration, degree, direction, disability, and distribution of this symptom. According to the study inclusion criteria, all patients displayed VAS pruritus values ≥ 5 (UVB nb, 7.2; UVB nb/UVA, 7.0), which corresponded well with high values for pruritus as assessed by the 5-D itch score (UVB nb, 20.9; UVB nb/UVA, 19.8). Before the start of treatment, no differences between both treatment groups could be detected for evaluation with either pruritus score (VAS, $p = 0.7491$; 5-D itch score, $p = 0.8241$) (Fig. 2a, b). After phototherapy, pruritus VAS scores declined (UVB nb, 2.0, $p < 0.0001$; UVB nb/UVA, 2.5, $p = 0.0001$) to similar levels of 27.96% (+/- SEM of 6.859%) for UVB nb alone and 35.21% (+/- SEM of 10.60%) for combined UVB nb/UVA. Correspondingly, 5-D itch score values declined (UVB nb, 10.5, $p < 0.0001$; UVB nb/UVA, 13.3, $p = 0.0038$) to similar levels of 50.45% (+/- SEM of 6.033%) for UVB nb alone and 67.00% (+/- SEM of 6.877%) for combined UVB nb/UVA. No difference could be observed between either treatment modality (VAS, $p = 0.4486$; 5-D itch score, $p = 0.1510$), suggesting that UVB nb and combination

UVB nb/UVA therapy are equally effective in relieving disease-associated pruritus. In order to confirm the validity of both tools, VAS and 5-D itch score values were correlated. For both treatment regimens, a high positive correlation could be observed (UVB nb, $r = 0.68$, $p = 0.0007$; UVB nb/UVA, $r = 0.71$, $p = 0.0182$) (Fig. 2c), thereby confirming the validity with which both scores assess pruritus as a subjective symptom. In order to investigate whether the reduction in pruritus scores was accompanied by a comparable reduction in disease activity, clinical scores (PASI, EASI, PSGA, DDV) were analyzed for both treatment regimens. Before the start of treatment, no difference in disease activity could be detected between both treatment groups ($p = 0.8651$) (Fig. 3; UVB nb, 12.9; UVB nb/UVA, 11.4). After phototherapy, disease activity scores were reduced (UVB nb, 2.2, $p < 0.0001$; UVB nb/UVA, 1.7, $p = 0.0005$) to similar levels of 17.44% (+/- SEM of 3.771%) for UVB nb alone and 14.89% (+/- SEM of 5.645%) for combined UVB nb/UVA. No difference between both treatment modalities could be observed ($p = 0.4323$). This indicates that UVB nb and UVB nb/UVA are equally effective in reducing disease activity within our patient collective.

In addition to clinical scores, questionnaires which assess the QoL are useful in order to obtain additional information on individual disease manifestation.[16] As inflammatory skin diseases can be accompanied by a strong impairment in QoL,[17] we investigated whether phototherapy led to an overall improvement within our study population. Notably, before the start of treatment, higher baseline DLQI values and a higher degree of impairment was observed within the UVB nb/UVA treatment group (DLQI 15.5), compared to the UVB nb treatment group (DLQI 11.2) (Fig. 4; $p = 0.0449$). After phototherapy, DLQI values were reduced (UVB nb, 5.8, $p = 0.0024$; UVB nb/UVA, 6.5, $p = 0.0023$) to similar levels of 51.57% (+/- SEM of 10.43%) for UVB nb alone and 42.23% (+/- SEM of 11.78%) for combined UVB nb/UVA, thus indicating a strong improvement in QoL for both treatment modalities ($p = 0.7034$). Due to the initially disparate baseline DLQI values in each group, the average reduction relative to their starting values was compared, but no difference could be determined ($p = 0.5776$). These findings suggest that UVB nb and UVB nb/UVA mediate an equally strong effect on the health-related QoL within our study population.

Discussion

Our study confirms the results from previous reports, which highlight the efficacy of UVB nb and combination UVB nb/UVA phototherapy for the treatment of inflammatory skin disease.[7, 8] In both treatment groups a reduction in pruritus, and disease activity could be observed, further accompanied by an improvement in QoL. However, no difference in efficacy – when considering each of the above 3 parameters - could be demonstrated between phototherapy with UVB nb or combination UVB nb/UVA.

While the exact modes of action for different types of UV phototherapy are still under investigation, an additive effect for UVA on UVB has been proposed.[18] In our clinical trial comparing these two modalities, the lack of superiority of combined UVB nb/UVA therapy over UVB nb alone argues against an additional benefit of UVA, compared to exclusive UVB nb therapy. However, given the size of our study groups, we cannot exclude a discrete additional effect of UVA within combination phototherapy. This possibility could be further investigated by comparing UVB nb/UVA with exclusive UVB nb treatment in future studies.

Several acute and chronic side effects have been associated with increased exposure to each type of UV radiation. Reactions include inflammation, local or systemic immunosuppression, photoageing, and carcinogenesis.[19] UVA in particular can induce DNA damage in skin cells via activation of endogenous photosensitisers, resulting in local oxidative stress.[20] In view of these cumulative side effects, the lacking evidence for clear superiority of combination UVB nb/UVA phototherapy, and the increased amount of treatment time as well as cost of treatment, the previously recommended addition of UVA should be abandoned. We thus recommend that the indication for combination UVB nb/UVA phototherapy should be critically scrutinised on an individual basis, in order to prevent exposing patients to side effects in the absence of additional therapeutic benefit.

In conclusion, our study underlines, as previously reported by others, the value of phototherapy in the treatment of pruritus associated with inflammatory skin disease. We have demonstrated that disease activity is effectively reduced by both UVB nb and combined UVB nb/UVA phototherapy. In addition, patients treated by phototherapy benefit from a strong improvement in health-related quality of life. However,

combination phototherapy does not provide a significant advantage as far as reduction of pruritus, disease activity and quality of life are concerned. In view of the indifferent efficacy of both treatment modalities, and the potential long term side effects of added UVA therapy, we recommend that the indications for combined UVB nb/UVA phototherapy should be handled restrictively.

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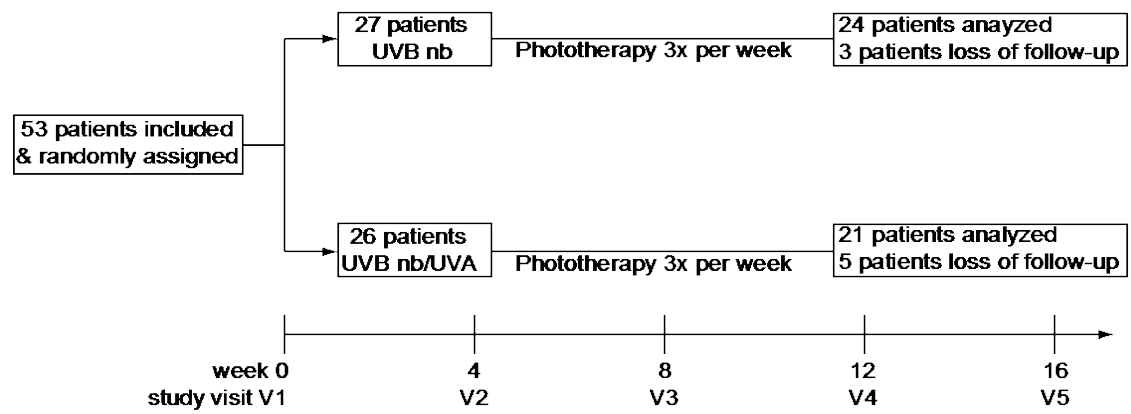


Figure 1

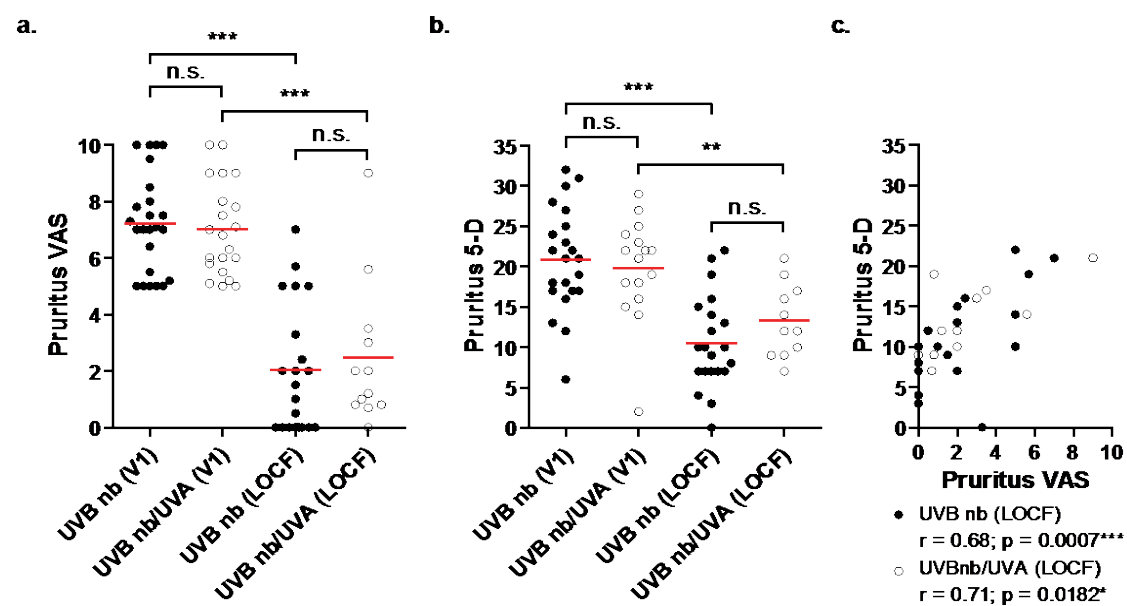


Figure 2

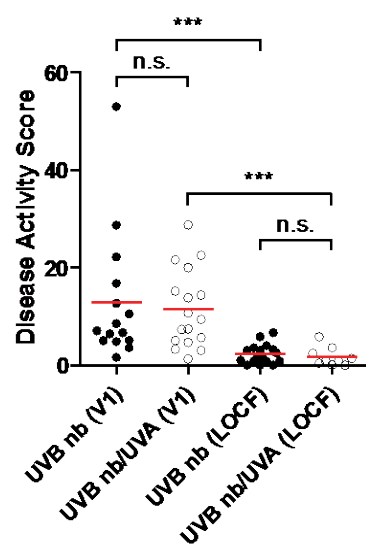


Figure 3

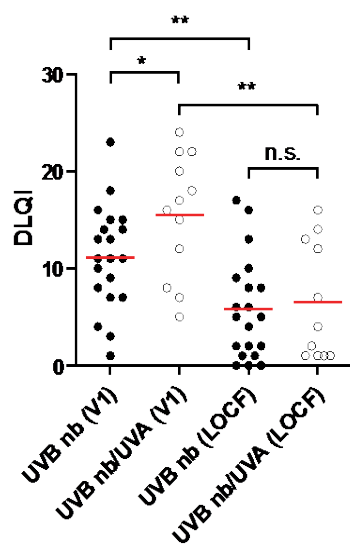


Figure 4

Table 1 Baseline characteristics of the patients

Characteristic*	Treatment group		Total n=53	P-Value
	UVB nb n=27	UVB nb/UVA n=26		
Age - years, median (range)	58.0 (23-83)	46.5 (19-75)	49.0 (19-83)	0.0995
Sex - no. (%)				0.4064
Male	18 (66.7)	14 (53.8)	32 (60.4)	
Female	9 (33.3)	12 (46.2)	21 (39.6)	
Height - m, median (range)	1.76 (1.58-1.88)	1.74 (1.55-1.92)	1.74 (1.55-1.92)	0.8938
Weight - kg, median (range)	80.0 (45.5-118.5)	72.6 (47.8-110.0)	76.8 (45.5-118.5)	0.2868
BMI** - kg m ⁻² , median (range)	26.8 (18.0-39.1)	24.2 (18.7-36.7)	25.9 (18.0-39.1)	0.0628
Fitzpatrick skin type - no. (%)				0.5243
Type I	-	-	-	
Type II	14 (58.3)	13 (56.5)	27 (57.4)	
Type III	10 (41.7)	8 (34.8)	18 (38.3)	
Type IV	-	1 (4.3)	1 (2.1)	
Type V	-	1 (4.3)	1 (2.1)	
Type VI	-	-	-	
History of phototherapy - no. (%)				0.5467
Positive	11 (45.8)	7 (35.0)	18 (40.9)	
Negative	13 (54.2)	13 (65.0)	26 (59.1)	
Diagnosis - no. (%)				0.1317
Eczema	11 (40.7)	16 (61.5)	27 (50.9)	
Atopic eczema	10 (37.0)	14 (53.8)	24 (45.3)	
Nummular eczema	1 (3.7)	1 (3.8)	2 (3.8)	
Unclassifiable eczema	0	1 (3.8)	1 (1.9)	
Psoriasis	10 (37.0)	4 (15.4)	14 (26.4)	
Prurigo simplex subacuta	1 (3.7)	4 (15.4)	5 (9.4)	
Pruritus sine materia	1 (3.7)	1 (3.8)	2 (3.8)	
Others***	4 (14.8)	1 (3.8)	5 (9.4)	

*Discrepancy from total number of included patients may reflect incomplete data acquisition; **BMI, body mass index; ***T cell lymphoma, Lichen planus, Folliculitis, Pityriasis lichenoides chronica, Prurigo nodularis.

Figure legend

Fig. 1 Study design. Patients included in the study were randomized 1:1 and either received phototherapy 3 times per weeks with UVB nb, or UVB nb/UVA. At baseline at the start of therapy, after 4, 8, 12, and 16 weeks patients were examined, and pruritus (VAS and 5-D itch score), disease activity (PASI, EASI, PSGA, DDV), and quality of life (DLQI) were assessed.

Fig. 2 Pruritus is effectively reduced after phototherapy with UVB nb or combination UVB nb/UVA. **(a)** Scatter plots depict pruritus VAS values for UVB nb (black circles) or combination UVB nb/UVA phototherapy (open circles), before the start of treatment (V1), and as the last-observation-carried-forward (LOCF). **(b)** As in (a), but for pruritus, as assessed by the 5-D itch score. **(c)** Scatter plots depict correlation of pruritus VAS and 5-D itch score values. * $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$ (Mann-Whitney test (a, b), Spearman nonparametric testing (c)).

Fig. 3 Disease activity is effectively reduced after phototherapy with UVB nb or combination UVB nb/UVA. Scatter plots depict the disease activity score for UVB nb (black circles) or combination UVB nb/UVA phototherapy (open circles), before the start of treatment (V1), and as the last-observation-carried-forward (LOCF). *** $P < 0.001$ (Mann-Whitney test).

Fig. 4 Quality of life is effectively improved after phototherapy using UVB nb or combination UVB nb/UVA. Scatter plots depict DLQI values for UVB nb (black circles) or combination UVB nb/UVA phototherapy (open circles), before the start of treatment (V1), and as the last-observation-carried-forward (LOCF). * $P < 0.05$, ** $P < 0.005$ (Student's t-test).

Table 1 Baseline characteristics of the patients